DETAILED ACTION

Election/Restrictions-Withdrawn in Part (Compound Election Converted to Species Election)

Applicant's election with traverse of Group I, claims 1-16, as drawn to the compound "z-VAD" in the reply filed on 3/31/10 is acknowledged. The traversal, relevant to the grounds for Lack of Unity, is that:

> "…as stated in MPEP 803.2 unity of invention exists where compounds included in a Markush group share a common utility ***and*** *share a substantial structural feature essential to that utility*. The common utility is the ability to inhibit apoptosis in a hematopoietic stem cell and the common structural feature is the structure for binding and inhibiting caspase."

The Examiner has considered Applicant's arguments and hereby converts the election of the compound "z-VAD" to an election of species; as opposed to an election of the invention. Where the elected species is found allowable, the search/examination will move on to other non-elected caspase inhibitors.

Additionally, upon a finding of allowability of a single caspase, the search/examination will move on to the combination invention of claims 10-16,

The requirement is still deemed proper and is therefore made FINAL.

Claims 10-16 are tentatively withdrawn from consideration as being drawn to administering a combination of caspase inhibitors or some other compound, in which art on the elected species invention of a single caspase inhibitor ("z-VAD") would not necessarily teach or render obvious the latter, or vice versa. Claims 1-9 are examined on the merits as being drawn to the elected invention, and species election of "z-VAD".

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goldmakher et al. (US 7,449,450).

Goldmakher et al. teach the use of the elected caspase inhibitor "z-VAD" as an effective inhibitor of apoptosis, and teaches that other uses of apoptosis inhibition are for hematopoietic cells and during non-desired apoptosis caused by radiation (see KWIC search below; entire document).

I. "z-VAD" Caspase Inhibitor

Description Paragraph - DETX (4):
FIG. 2A is a histogram showing the effects of TNF-.alpha. and anti-Fas antibody, alone or in the presence of CHX, or CHX+ the caspase inhibitor Z-VADfmc, on the survival of MRC-5 normal human fibroblasts 24 h and 48 h after treatment, as measured by direct observation and quantitation of cells under a phase microscope.

Description Paragraph - DETX (82):
In a preferred embodiment, HeLa cells transfected with a viral polynucleotide, encoding a polypeptide, are exposed to the anti-Fas monoclonal antibody 7C11+CHX or to TNF-.alpha.+CHX, and cell death is measured by visual scoring of the cells under a phase microscope. Alternatively, the induced cell death or apoptosis of the HeLa cells, can be examined by a dye-exclusion test on a flow cytometer. Fas-mediated apoptosis is accompanied by the characteristic apoptotic events: 1) surface blebbing, as observed under a phase microscope (not shown); 2) emergence of phosphatidylserine, an early marker of apoptosis in the outer layer of the cell plasma membrane; 3) DNA degradation (not shown); and 4) protection by a caspase inhibitor, for example, Z-VADfmc.

Description Paragraph - DETX (312):
Both Fas- and TNF-R1-mediated MRC-5 cell death exhibited typical features of apoptosis such as the emergence of phosphatidylserine in the outer layer of the cell plasma membrane, surface blebbing, and DNA degradation, and was prevented by the caspase inhibitor Z-VADfmk. For example, anti-Fas antibody-induced cell death of MRC-5 cells was examined by a dye-exclusion test on a flow cytometer (FIG. 2B), and the results were consistent with those obtained by visual microscopic examination. Fas-mediated cell death was accompanied by the characteristic apoptotic events such as: 1) surface blebbing, as observed under a phase microscope (not shown); 2) emergence of phosphatidylserine, an early marker of apoptosis in the outer layer of the cell plasma membrane (FIG. 2C); 3) DNA degradation (not shown); and 4) protection by the caspase inhibitor Z-VADfmc (FIGS. 2A-2C).

II. Preferred Cells being Hematopoietic

Preferred Method: Modulating apoptosis results in enhanced or reduced stability, growth, and/or productivity of the eukaryotic cell. The cell is a target cell in a patient and the contacting is ex vivo contact comprising isolating the target cell from the patient, establishing the target cell in a culture, transfecting the target cell with a synthetic or viral vector comprising a polynucleotide encoding the polypeptide, the fragment or homologue, and returning the target cell to the patient. The viral vector is a retrovirus vector, adenovirus vector, adeno-associated virus vector, vaccinia virus vector, herpes simplex virus vector, avipox virus vector, or baculovirus vector. The compound is an isolated or synthetic antibody that hinds to pUL37s or its fragment. The antibody is a polyclonal or monoclonal antibody. The compound is a synthetic peptide, selectively binds to viral polypeptide and not cellular polypeptide, and is an anti-sense oligonucleotide that comprises an anti-sense oligonucleotide having a phosphorothioate backbone. The cell, prior to the contacting, has disregulated or aberrant apoptotic activity caused by a

degenerative disorder having inappropriate cell death or inappropriate cell proliferation, such as a cancer, immune disorder, autoimmune disease, infectious disease, viral infection, or myocardial infarction or neuronal infarction in cardiovascular disease. The viral infection is a Cytomegalovirus infection. The cell, prior to the contacting, also has apoptotic activity potentiated or mediated by Fas receptor, tumor necrosis factor receptor 1, or an activator of a signal transduction pathway that results in apoptosis. The polypeptide, fragment or homologue inhibits or diminishes one or more of the activation of caspase 9, the release of cytochrome c from mitochondria, the activity of adenine nucleotide translocator, or preferably the activation of caspase 8. The contacting is by pressure-mediated delivery, preferably by a gene gun, liposome delivery or by ex vivo. The cell is a hybridoma, a fibroblast, a lymphoid cell, a hematopoietic cell, a cell derived from an embryonic central nervous system, or a cell derived from normal, dysplastic, or neoplastic tissue. The fragment comprises amino acid residues 5-34 and 118-147 of pUL37s, preferably amino acid residues 118-147 of pUL37s. The homologue of pUL37s has at least 90% sequence identity with the native form of pUL37s.

III. Inhibiting Apoptosis during Radiation

Description Paragraph - DETX (210):
Premature widespread apoptosis (inappropriate cell death) causes much of the damage associated with degenerative disorders or diseases including, for example, AIDs, chemotherapy and radiation, and tissue atrophy. In AIDs patients, lymphocytes are activated even in the asymptomatic phase of the HIV infection, and those cells die prematurely by apoptosis. Such disorders may be treated by delivery of compounds of the invention that inhibit or diminish apoptosis, such as polypeptides having anti-apoptotic activity or polynucleotides encoding such polypeptides.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the elected caspase inhibitor of "z-VAD" for treating hematopoietic stem cells during radiation exposure in Goldmakher et al., because Goldmakher et al. advantageously teaches, specifically, the ability of the elected "z-VAD" to inhibit apoptosis, as well as teaches that a preferred type of cell contemplated is "hematopoietic cells" and that a preferred event for inhibiting apoptosis is during radiation exposure. It would have been routine

optimization by the skilled artisan to understand that the same would apply to hematopoietic "stem" cells and that inhibiting their exposure during undesired apoptosis as a result of radiation would be a natural desire. And based on the results of Goldmakher et al, "z-VAD" would be the immediate choice of caspase inhibitor to carry out the same; absence evidence to the contrary of some unexpected result.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the reference, especially in the absence of evidence to the contrary.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MAURY AUDET whose telephone number is (571)272-0960. The examiner can normally be reached on M-Th. 7AM-5:30PM (10 Hrs.).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MA, 4/26/2010

/Maury Audet/
Primary Examiner, Art Unit 1654